RESPONSE

I. Status of the Claims

No claims have been cancelled. No claims have been amended. No new claims have been added.

Claims 1 and 3-20 are therefore presently pending in the case.

II. Support for the Amendment

The specification has been amended to include a new title that is more descriptive of the invention to which the claims are directed. Support for the new title can be found in the original title, and throughout the specification and claims as originally filed.

It will be understood that no new matter is included within the new title.

III. Title

The Action objects to the title of the application based on the term "novel". Applicants have amended the title of the present application to remove the term "novel".

Applicants request that, since the objection has been overcome, this objection be withdrawn.

IV. Rejection of Claims 16-20 Under 35 U.S.C. § 101

The Action first rejects claims 16-20 under 35 U.S.C. § 101, as allegedly drawn to non-statutory subject matter. Applicants respectfully traverse.

The Examiner states that claims 16-20 are non-statutory because "the claims as written read on a transgenic human" (the Action at page 3). Applicants respectfully point out that at page 20, line 16, the present specification specifically contemplates "non-human primates" as transgenic animals, and thus specifically disclaims human transgenic animals. Therefore, the Examiner's reasoning is misplaced, and the rejection of claims 16-20 under 35 U.S.C. § 101 as allegedly drawn to non-statutory subject matter should be withdrawn.

Furthermore, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable (*State Street Bank & Trust Co. v. Signature Financial Group*

Inc., 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)). Furthermore, as the Office has issued **thousands** of patents directed simply to "host cells", Applicants submit that claims 16-20, which are also directed to a host cell, **must** be statutory. Specifically, on June 22, 2004 **alone**, approximately one month before the Action was issued, the Office issued U.S. Patent Nos. 6,753,163, 6,753,176, 6,753,177, and 6,753,419, each of which has at least one claim directed to "a host cell". Therefore, the rejection of claims 16-20 as non-statutory is arbitrary and capricious, and cannot stand.

Applicants therefore request that the rejection of claims 16-20 under 35 U.S.C. § 101 be withdrawn.

V. Rejection of Claims 1 and 3-20 Under 35 U.S.C. § 101

The Action first rejects claims 1 and 3-20 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

The present invention has a number of substantial and credible utilities, not the least of which is in forensic biology, as described in the specification, at least at page 4, lines 30-33. As described in the specification, at page 8, lines 17-23, the present sequences define two coding single nucleotide polymorphisms - specifically: a silent T/C polymorphism at nucleotide position 3601 of SEQ ID NO:1, both of which result in a threonine residue being present at the corresponding amino acid (aa) position 1201 of SEQ ID NO:2; and a silent T/C polymorphism at nucleotide position 2173 of SEQ ID NO:3, both of which result in a threonine residue being present at the corresponding aa position 725 of SEQ ID NO:4. As such polymorphisms are the basis for forensic analysis, which does not require the identification of a specific medical condition, and is undoubtedly a "real world" utility, the present sequences must in themselves be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner states that "(n)either the specification nor the art of record disclose any diseases or conditions associated with the function or expression of the NGPCR protein, therefore, there is no 'real world' context of use" (the Action at page 4). First, Applicants point out that the disclosure of "any diseases or conditions associated with the function or expression of the NGPCR protein" is not the standard for patentability under 35 U.S.C. § 101 (*In re Brana*, 34 USPQ2d 1436 (Fed. Cir.

1995); "*Brana*"). Furthermore, Applicants reiterate that the use of the presently described polymorphisms in forensic analysis does **not** require the identification of a specific medical condition. One aspect of forensic analysis is to distinguish individual members of the human population from one another based solely on the **presence** or **absence** of one or more polymorphic markers, such as the presently described polymorphisms. As polymorphic markers such as the presently described polymorphism have been used in forensic analysis for decades, this is clearly a well established technique, and as such, specific guidance does not need to be provided in the present specification, for it has long been established that a patent need not disclose what is well known in the art (*In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988)). Thus, the Examiner's argument does not support the alleged lack of utility.

This is also not a case of a "potential" utility. Using the polymorphic markers exactly as described in the specification as originally filed, the skilled artisan can readily distinguish individuals from one another. Applicants point out that in the worst case scenario, each polymorphic marker is useful to distinguish 50% of the population (in other words, the marker being present in half of the population). This is an inherent feature of any polymorphic marker, as the largest percentage of a population that two polymorphic markers can define is 50% each. If a polymorphic marker is present at a level of less than 50%, then that marker is even **more** informative, *i.e.*, a **greater** percentage of the population can be distinguished on the basis of the marker. Nevertheless, the ability to eliminate even 50% of the population from a forensic analysis clearly is a real world, practical utility.

Furthermore, with regard to a "'real world' context of use", Applicants point out that naturally occurring genetic polymorphisms such as the polymorphisms described in the specification as originally filed are both the basis of, and critical to, *inter alia*, forensic genetic analysis intended to resolve issues of, for example, identity or paternity. Forensic analysis based on polymorphisms such as the polymorphisms identified by Applicants is used to positively identify or rule out suspects in many criminal cases, and in identifying human remains. Paternity determination is based on polymorphisms such as the polymorphisms identified by Applicants to positively identify or rule out individuals suspected of fathering a particular child. What could be possibly be more substantial and "real world" than the loss of an individual's freedom or life through incarceration? What could be possibly be more substantial and "real world" than the positive identification of human remains? What could be possibly

be more substantial and "real world" than the impact, both economic and emotional, that the results of a paternity analysis has on the individuals directly and indirectly involved? These are all well known and generally accepted uses of polymorphisms such as the polymorphisms identified by Applicants. Without such identified polymorphisms, the skilled artisan would not be able to carry out such forensic or paternal analyses. Therefore, as the use of the presently described polymorphic markers in forensic analysis is clearly a "real world" and substantial utility, the presently claimed sequences meet the requirements of 35 U.S.C. § 101.

The Examiner next states that "(f)urther research to identify or reasonably confirm a 'real world' context of use is required" (the Action at page 4). First, Applicants reiterate that the use of the presently described polymorphic markers in forensic analysis, as detailed above, requires **no** further research. Thus, the presently described polymorphisms can be used to distinguish individuals from one another in their currently available form. Second, Applicants respectfully point out that the proper standard for meeting the requirements of 35 U.S.C. § 101 is **not** whether "further research" is required to practice certain aspects of the claimed invention, but whether **undue** experimentation would be required to practice the claimed invention. The widespread use of polymorphisms such as those described by Applicants in forensic analysis every day **strongly** argues against such a use requiring "undue experimentation". Applicants point out that in assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). However, even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana* (*supra*), which states that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added). Thus, the need for some experimentation clearly does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin*, *supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Applicants respectfully point out that as the presently described polymorphisms are a part of

the family of polymorphisms that have a well-established utility, the Federal Circuit's holding in *Brana* (*supra*) is directly on point. In *Brana*, the Federal Circuit admonished the United States Patent and Trademark Office ("the USPTO") for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. Thus, based on the holding in *Brana*, the present claims meet the requirements under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph (see Section VI, below).

It is important to note that it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As clearly set forth in *Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of

> utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the Manual of Patent Examining Procedure ("MPEP"), "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Therefore, absent evidence from the Examiner that the presently described polymorphic markers could not be used in forensic analysis, as the skilled artisan would readily understand that the present polymorphic markers have utility in forensic analysis, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner states that the invention lacks a patentable utility because the specification "does not disclose the biological role of this protein or its significance" (the Action at page 3). Applicants disagree, as the presently claimed sequences are clearly referred to as G-protein coupled receptors ("GPCRs"; see, at least, the specification at page 2, lines 8-11), and further, that such GPCRs "are typically involved in transduction pathways involving G-proteins or PPG proteins" (specification at page 2, lines 2-3). Furthermore, Applicants would like to invite the Examiner's attention to the fact a sequence sharing nearly 100% percent identity at the protein level over nearly the full length of the claimed sequences (discounting the three non-shared exons likely arising from differential splicing) is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists *wholly unaffiliated with Applicants* as "Homo sapiens G-protein coupled receptor GPR112" (GenBank accession number NM_153834; alignment and GenBank report provided in **Exhibit A**). Furthermore, Applicants respectfully point out that GPR112 has been classified as an adhesion GPCR (Fredriksson *et al.*, *FEBS Lett.* **531**:407-414, 2002, and Bjarnadottir *et al.*, *Genomics* **84**:23-33, 2004; abstracts provided in **Exhibit B**). Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55; **Exhibit C**), which have been set forth by the USPTO, clearly establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility, and under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility (see Section VI, below), is not proper when a full length sequence (such as the presently claimed sequence) has a similarity score

greater than 95% to a protein having a "well established utility". Therefore, as the present situation tracks Example 10 of the Revised Interim Utility Guidelines Training Materials, the USPTO's own examination guidelines clearly indicate that the present claims meet the requirements of 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph (see Section VI, below). Thus, the present rejection of claims 1 and 3-20 should be withdrawn.

The Examiner goes on to cite a number of scientific articles to support the present rejection. The Examiner first cites an article by Doerks *et al.* (*Trends in Genetics* **14**:248-250, 1998) for the proposition that sequence-to-function methods of assigning protein function are prone to errors. However, Doerks *et al.* states that "utilization of family information and thus a more detailed characterization" should lead to "simplification of update procedures for the entire families if functional information becomes available for at least one member" (Doerks *et al.*, page 248, paragraph bridging columns 1 and 2, emphasis added). Applicants point out that, as detailed above, a sequence sharing nearly 100% percent identity at the protein level over nearly the full length of the claimed sequences is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists *wholly unaffiliated with Applicants* as an adhesion GPCR (see **Exhibits A** and **B**). The adhesion GPCRs are a well-studied protein family with a large amount of known functional information, exactly the situation that Doerks *et al.* suggests will "simplify" and "avoid the pitfalls" of previous sequence-to-function methods of assigning protein function (Doerks *et al.*, page 248, columns 1 and 2). Thus, instead of supporting the Examiner's position against utility, Doerks *et al.* actually supports Applicants' position that the presently claimed sequences have a substantial and credible utility.

The Examiner next cites Brenner (*Trends in Genetics* 15:132-133, 1999) as teaching that "most homologs must have different molecular and cellular functions" (the Action at page 3). However, this statement is based on the assumption that "if there are only 1000 superfamilies in nature, then most homologs must have different molecular and cellular functions" (Brenner, page 132, second column). Furthermore, Brenner suggests that one of the main problems in using homology to predict function is "an issue solvable by appropriate use of modern and accurate sequence comparison procedures" (Brenner, page 132, second column), and in fact references an article by Altschul *et al.*, which is the basis for one of the "modern and accurate sequence comparison procedures" used by Applicants.

Thus, the Brenner article also does not support the alleged lack of utility.

The Examiner finally cites Bork *et al.* (*Trends in Genetics* **12**:425-427, 1996) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable, based on the "structural similarity of a small domain of the new protein to a small domain of a known protein" (the Action at page 3). However, the Examiner's reliance on Bork *et al.* is based on a faulty assumption, specifically, the assumption that Applicants' assertion that the present sequence is a GPCR is made on the basis of structural similarity of a small domain of the new protein to a small domain of a known protein. Applicants again would like to invite the Examiner's attention to the fact a sequence sharing nearly 100% percent identity at the protein level over nearly the full length of the claimed sequences is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists *wholly unaffiliated with Applicants* as an adhesion GPCR (see **Exhibits A** and **B**). Thus, Applicants assertion that the present sequence is a GPCR is not made on the basis of "structural similarity of a small domain of the new protein to a small domain of a known protein", but rather vast homology over a large tract of the sequence. Thus, Bork *et al.* also does not support the alleged lack of utility for the present invention.

Furthermore, notwithstanding the deficiencies detailed above, with regard to the citation of art to support the present rejection under 35 U.S.C. § 101, Applicants first note for the record that scientific manuscripts from 1996, 1998, and 1999 can hardly be considered to reflect the state of the art at the time the present application was filed. Second, and more importantly, such citations reflect that the Examiner appears to believe that extensive structural similarity is not enough to establish a specific utility. Applicants respectfully point out the Examiner's position **directly contradicts** the position of the USPTO itself, as set forth in Example 10 of the Revised Interim Utility Guidelines Training Materials (see **Exhibit C**), which clearly establishes that structural similarity **can** in fact be used to establish function, and thus establish a specific utility. Therefore, as the USPTO's **own** examination guidelines clearly indicate that structural similarity **can** in fact be used to establish function, and thus establish a specific utility, the present claims meet the requirements of 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph (see Section VI, below), and the present rejection of claims 1 and 3-20 should be withdrawn.

Applicants respectfully point out that of the pharmaceutical products currently being

marketed by the entire industry, 60% of these products target G-protein coupled receptors (Gurrath, *Curr. Med. Chem.* **8**:1605-1648, 2001; abstract provided in **Exhibit D**). Given that more than half of the currently marketed drugs target proteins that are structurally (7TM proteins) and functionally (G-protein interaction) related to the presently described sequences, a preponderance of the evidence clearly weighs in favor of Applicants' assertion that the skilled artisan would readily recognize that the presently described sequences have a number of specific (the claimed GPCR proteins are encoded by a specific locus on the human genome), credible, and well-established utilities in addition to those detailed above, for example in tracking gene expression. As the specification as originally filed details on page 10, lines 6-9, the present nucleotide sequences have utility in assessing gene expression patterns using high-throughput DNA chips. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305 (**Exhibits E-G**; submitted with the Information Disclosure Statement filed on March 22, 2002), and U.S. Patent Nos. 5,837,832, 6,156,501 and 6,261,776 (**Exhibits H-J**; copies of issued U.S. Patents not provided pursuant to requests from the USPTO). As the present sequences are specific markers of the human genome (see below), and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful.

Further evidence of the "real world" substantial utility of the present invention is provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company (Rosetta Inpharmatics) was viewed to have such "real world" value that it was acquired by large a pharmaceutical company (Merck) for

significant sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, *Science* **291**:1304, 2001; **Exhibit K**). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, *Science* **291**:1153, 2001; **Exhibit L**). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Applicants respectfully point out that only expressed polynucleotide sequences can be used to track gene expression, not just any polynucleotide. Furthermore, expression profiling does not even require a knowledge of the function of the particular nucleic acid on the chip - rather the gene chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular tissue types. Skilled artisans already have used and continue to use sequences such as Applicants in gene chip applications without further experimentation. Importantly, the requirement for a specific utility, which is the proper standard for utility under 35 U.S.C. § 101, should not be confused with a requirement for a unique utility, which is clearly an improper standard. As clearly set forth by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991; "*Carl Zeiss*"):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Following directly from the quote above, an invention does not need to be the only way to accomplish a certain result. Thus, the question of whether or not other nucleic acid sequences can be used to assess gene expression patterns is completely irrelevant to the present utility inquiry. The only relevant

question in regard to meeting the standards of 35 U.S.C. § 101 is whether every nucleic acid sequence can be so used - and the clear answer to this question is an emphatic **no**. Importantly, the holding in *Carl Zeiss* is mandatory legal authority that essentially controls the outcome of the present case. Furthermore, the requirement for a unique utility is clearly not the standard adopted by the USPTO. If every invention were required to have a unique utility, the USPTO would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer and bacterial or viral infections, just to name a few particular examples, because examples of each of these have already been described and patented. All batteries have the exact same utility - specifically, to provide power. All automobile tires have the exact same utility - specifically, for use on automobiles. All golf balls and golf clubs have the exact same utility - specifically, use in the game of golf. All cancer treatments have the exact same utility - specifically, to treat cancer. All anti-infectious agents have the exact same broader utility - specifically, to treat infections. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions every week. Additionally, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Applicants respectfully point out that the generic class with regard to the present invention is "**all** nucleic acid sequences". Therefore, in determining whether an asserted utility is "generic" or "specific", it is improper to narrow the generic class of the invention to include only those subset of nucleic acids that have the asserted utility (for example, in the case above, nucleic acids that are expressed) in order to support an allegation that the claimed nucleic acids lack a "specific" utility. With regard to the asserted utility of assessing gene expression patterns using high-throughput DNA chips, Applicants respectfully point out that only 2-4% of all nucleotide sequences are expressed. Therefore, the question of whether the asserted utility is "specific", as opposed to "generic", has clearly been laid to rest. Therefore the present claims are clearly in compliance with 35 U.S.C. § 101.

It has been well established that Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983);

In re Gottlieb, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), and, thus, any questions concerning whether or not the present claims meet the requirements of 35 U.S.C. § 101 should have been laid to rest. Nevertheless, as a further example of the utility of the presently claimed polynucleotides, as described in the specification at page 4, lines 23-26, the present nucleotide sequences have a specific utility in "identification of protein coding sequences" and "mapping unique genes to one or more particular chromosome". The specification as originally filed, at page 4, lines 26-27, details that the gene encoding the presently claimed sequences is "X-linked, see GENBANK accession no. AL161778". In fact, alignment of SEQ ID NO:1 with GenBank Accession Numbers AL161778 and AL136167 (which are overlapping genomic clones from the human X chromosome) shows that the human gene corresponding to SEQ ID NO:1 is dispersed on 20 exons of the human X chromosome (alignment and the first pages from the GenBank reports are presented in **Exhibit M**). In fact, **both** of these GenBank reports note the presence of the presently claimed GPCR sequence (GPR112) within this stretch of genomic sequence. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human X chromosome that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence. For further evidence in support of the Applicants' position, the Examiner is requested to review, for example, section 3 of Venter *et al.* (*supra*, at pp. 1317-1321, including Fig. 11 at pp.1324-1325; see **Exhibit K**), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Applicants reiterate that only a minor percentage (2-4%) of the genome actually encodes

exons, which in-turn encode amino acid sequences. Significantly, the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). As described in the specification as originally filed at page 4, lines 27-30, the claimed "sequences identify actual, biologically relevant, exon splice junctions, as opposed to those that might have been predicted bioinformatically from genomic sequence alone". The specification as originally filed, at page 15, lines 17-22, further details that "sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics". Applicants respectfully submit that the practical scientific value of biologically validated, expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Applicants once again point out that only expressed sequences can be used in the identification of coding sequence, not just any polynucleotide. Second, Applicants reiterate that the requirements of a specific utility, which is the proper standard for utility under 35 U.S.C. § 101, should not be confused with the requirement for a unique utility, which is clearly an improper standard (*Carl Zeiss*, *supra*). The fact that a small number of other nucleotide sequences could be used to map the protein coding regions in this specific region of the human X chromosome does not mean that the use of Applicants' sequence to map the protein coding regions of the human X chromosome is not a specific utility. Once again, the question of whether or not other nucleic acid sequences can be so used is completely irrelevant to the present utility inquiry. The only relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every** nucleic acid sequences can be so used - and the clear answer to this question is once again an emphatic **no**. Applicants respectfully point out that the generic class of "**all** nucleic acid sequences" cannot be narrowed to include only the small number of nucleic acid molecules that are expressed from this particular region of the human X chromosome in order to support an allegation that the claimed nucleic acids lack a "specific" utility. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Lastly, the Examiner cites *Brenner v. Manson* (383 U.S. 519, 148 USPQ 689 (S. Ct. 1966);

"*Brenner*") to support the alleged lack of utility. However, the Federal Circuit, citing *Brenner*, recently affirmed that "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit has emphatically confirmed that "anything under the sun that is made by man" is patentable (*State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)). Thus, all of the evidence presented above and the relevant case law, including that cited by the Examiner, supports the Applicants' assertion that the presently claimed sequences have a patentable utility, and are thus fully compliant with the requirements of 35 U.S.C. § 101.

Finally, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the USPTO itself for compliance with 35 U.S.C. § 101. While Applicants are well aware of the new Utility Guidelines set forth by the USPTO, Applicants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Applicants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As just a few examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides; **Exhibits N-P**; copies of issued U.S. Patents not provided pursuant to requests from the USPTO), and U.S. Patent No. 6,340,583 (which includes no working examples;